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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	5

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applic...(s)
09/484,331	Harrington et al5
Examiner	**Group Art Unit**
Ram Shukla	1632

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *58-61* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *58-61* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Priority

1. This application is a division of Application No. 09/276,820, filed 3-26-1999.

2. Claims 58-61 are pending in the instant application.

Claim Rejections - 35 U.S.C. § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 58-61 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 58-69 are drawn to methods of drug discovery comprising steps of: integrating a vector into the genome of an eukaryotic cell that results in activation of an endogenous gene, culturing said cells under conditions, for example under reduced serum concentration, such that the product of the activated gene is produced, treating the cell with test compound(s) and screen for compounds by determining the ability of the test compound to interact with or affect a cellular phenotype induced by said gene product. Claim 60 limits the method of claim 59 to further comprise concentration of said cells' conditioned media before drug screening. Claim 61 limits the method of claim 59 to further comprise isolation of said gene product prior to screening.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the

claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue".The specification is not enabling for the claimed invention because the specification does not provide sufficient guidance, evidence or exemplification so that an artisan of skill would have been able to make and use the invention as claimed invention without undue experimentation.

In the instant case, claimed method encompasses, integrating a vector in a eukaryotic cell's genome to activate an endogenous gene, growing the cell so that the protein encoded by the activated gene is produced, treating the cells directly, with one or more test compounds to determine if compound(s) affect or interact with the phenotype associated with said gene expression. The claimed method also encompasses by first concentrating the conditioned media or isolating the protein before screening the test compounds and this is interpreted to encompass interaction of the protein encoded by said endogenous gene and a candidate compound in vitro. However, the specification is not enabling for the claimed invention because the specification fails to provide any guidance, working example or evidence as to how an artisan of skill would have practiced said drug discovery methods without undue experimentation.

While the specification has provided, diagrams of vectors that comprise claimed sequence elements and protocols to make libraries, PCR and other techniques of making cell lines, library etc., there is no evidence that all the claimed endogenous genes would have been activated by the claimed methods and would have yielded increased production of proteins from endogenous genes listed. On page 135 of the specification, lines 9-30 continued on page 136 lines 1-3 disclose the results of an experiment of activating expression of transmembrane protein. The specification discloses that in one screening, of eight isolated activated genes 4 encoded known integral membrane protein genes whereas 6 encoded novel genes (lines 10-13, page 135). In yet another example, the specification discloses that of 11 genes isolated, one had sequence homologous to a partially sequenced integral membrane protein gene whereas 9 were novel genes, for which nothing is known.

Caporale LH (Proc. Natl. Acad. Sci. USA. 92: 75-82, 1995) reviewed some aspects of drug discovery and stated, "A key step in the process of selecting a molecular target for a drug discovery program involves a demonstration that altering the activity of the proposed target should affect the disease." In the instant case, when the expression of an unknown gene is activated and there is some change in the phenotype of the cell, in the absence of any clues as to what disease such a phenotype or activated gene is related to how would a drug or compound be selected for determining whether it affected said phenotype. Caporale further argued,

> "Different receptor subtypes may couple the action of the signaling ligand (which might be a hormone or a neurotransmitter) to different second messenger system (e.g., activating adenyl cyclase or opening a potassium channel). Subtypes typically have distinct tissue distribution..... Consequently, the effect of drugs designed to selectively activate or inhibit one subtype can be confined to a subset of the functions of the endogenous ligand. Many sides effects of older drugs are caused by binding to nontarget subtypes. Therefore, selecting one subtype as a target and conunterscreening against nontarget subtypes provides a rational approach to broaden the window between efficacy and side effects.

Again the specification does not disclose any information how these types of controls would have been designed and what if there were no subtypes of a gene product identified during the practice of the claimed methods, how would an artisan have dealt with this limitation without undue experimentation because the artisan has to first characterize the gene activated, its protein's functions, its localization in a cell and what parts of the protein are important for its function before it could proceed to the step of compound testing.

Therefore, the main issue is: if the artisan did not know what gene has been activated how would the artisan test for the activity of a drug because for what activity is the artisan going to look for, in other words how would an artisan know that a given phenotype is because of one activated gene or more than one activated gene or whether the phenotype produced is the result of the expression of one gene alone that in turn may be activating multiple genes, for example, in a signal transduction pathway. In fact, the specification does not provide any guidance as to how an artisan would have carried out steps (c) and (d) of the the claimed method of drug discovery. Even when a certain known is targeted for drug screening, there are several limitations. For

example, Czerwinski et al (Czerwinski et al. Proc. Natl. Acad. Sci. USA. 95:11520-11525, 1998) reviewed the requirements of screening a successful drug for targeting of the receptors on tumor cells and noted,

> "Also one would expect that multiple drug resistance would be less important in the cease of cell surface-mediated active transport of drug across cell membrane. However, there are also many problems associated with this approach. One is to identify receptors that are present predominantly on tumor cells and in sufficient density. Another is that, until recently, little was known about the mechanisms and dynamics of receptor trafficking after ligand binding. ....Furthermore, very little is known about the fate of the internalized ligand-receptor complex.....It is crucial for successful drug delivery by the receptor-mediated route that the drug moiety attached to the ligand does not dominate the transport properties of the complex. For example, the lack of success in targeting opioid receptor-positive cells by an enkephalin-ellipticine conjugate was caused by the drug entering cells unspecifically."

Since the specification does not disclose any guidance regarding the characteristics of the gene being targeted and the drug being used, an artisan would not have known whether and how the transport and uptake of a candidate drug across cell membrane or binding to the receptor or ligand would have affected and therefore would have required undue experimentation to figure out these limitations of the method.

Further, what if the protein produced is not a full length protein, how would an artisan know what to screen for or what if the integration of the vector results in the expression of a protein that has inhibitory activity for a given function, how would the artisan know what to look for or how to monitor a phenotype of a cell. For example, what kind of phenotype will be monitored or by what method because if the expression of a gene results in transformation of a cell to a cancerous state what criteria an artisan would have taken to screen for the compound because transformation may be as a result of many steps and may not necessarily be correlated with one gene's activity. In summary, the method will be like a fishing expedition without knowing whether any gene or what gene would be isolated, identified, or characterized. As discussed above, there is no way of knowing what genes will be activated and therefore, an artisan has to characterize the gene expressed or activated before the drug discovery steps. In case of a

partial protein or gene being isolated, an artisan has to isolate and characterize the full length protein and at the end the phenotype due to the partial protein and full length protein may not be same.

Next, claimed methods encompass drug screening after concentrating conditioned medium of the cell or isolating the protein encoded by the activated gene, and then screening for drugs, in other words, incubating the isolated protein or the concentrated conditioned medium with the drug. Without knowing the nature of the protein encoded how would an artisan have known what kind of compounds to test. For example, without knowing the hydrophobic or hydrophilic nature of the protein, how would an artisan determine the assay conditions for the interaction of the protein or the drug. Again if a partial protein or sequence was isolated characteristics of the full length protein may be completely different than that of the partial protein and the assay conditions for a partial protein or protein fragment may be completely different from those for the corresponding full length protein. In other words, the specification does not provide any guidance as to how an artisan would have practiced the claimed methods without undue experimentation.

Next, let's suppose a gene was activated which has a known motif, even in this case, unless the function of the protein is known, how would an artisan know whether the phenotype is due to this transmembrane protein or due to the disrupted expression of another gene that is downstream in a cascade of pathways. If so how would an artisan know what kind of compounds to screen for without knowing what the gene does. Again the specification has not provided any guidance regarding these limitations of the method.

Next, even in the case of a transmembrane protein, while the specification discloses that four of the identified genes were transmembrane genes, there is no disclosure or evidence as to how many fold the expression of the isolated gene was increased or in fact whether there was any increase in the expression because the effect of the activated gene product may vary depending on how much encoded protein was produced and this would in turn affect the phenotype of the cell. The specification does not provide any guidance or example as to how an artisan would have dealt with this situation.

If the protein was expressed at low levels and the conditioned media was concentrated, would the protein still have been active because it is known in the prior art that proteins may lose their function or activity may decrease significantly when the proteins are concentrated. One has to realize that the cell growth medium may have inhibitors of the said protein or other enzymes such as proteases that may degrade the candidate protein. The specification does not provide any guidance as to how an artisan of skill would have dealt with this limitation of the method without knowing the characteristics of the protein. Additionally, isolation of the gene product or protein, if it is part of a large multi-protein complex, may also alter the activity of the protein and in such a case how would an artisan have known what method to use to preserve the activity of the protein.

Next, in case of methods, where the conditioned media is concentrated or the gene product is first isolated before screening for the target compounds, how would the change or alteration in the activity of the protein or gene product due to the interaction with the test compound would have been correlated with the phenotypic changes in the cell when the protein or gene was expressed in the cell. Again the specification does not provide any guidance as to how the results of interacting a test compound with the concentrated culture media or with isolated proteins will be correlated with the phenotype of cells wherein the gene was activated due to vector integration.

Next, if an artisan did not know the function of the gene activated, how would the artisan correlate the phenotype to its function. Additionally, if the function of the gene is not known how would an artisan correlate it to any disease and how would the artisan correlate the phenotype due to activated gene expression to the phenotype or symptoms of a disease because ultimately the goal would be treat a disease. However, if there is no correlation between the etiology of a disease with the phenotype of cells in culture that have an endogenous gene activated, how would an artisan screen for drugs that would alter the phenotype associated with certain unknown gene. The specification does not provide any guidance or example as to how an artisan would have dealt with these limitations.

In light of the above discussion, it is concluded that the specification is not enabling for the claimed invention because the specification does not provide sufficient guidance, evidence or exemplification so that an artisan of skill would have been able to make and use the claimed invention without undue experimentation.

5. Claims 58-61 are free of prior art on record.

6. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Thursday and every other Friday from 8:00 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached on (703) 308-2035. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 305-0196.

Ram R. Shukla, Ph.D.

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Ram R. Shukla, Ph.D.

JASEMINE CHAMBERS
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600